REMARKS

Claims 1-6 and 9-13 are currently under consideration. Applicant has amended claims 5, 6, and 10 to correct spelling errors. Claim 11 has been amended to recite method steps and claims 12 and 13 to be in parallel form with claim 11. Applicant also amended claims 3, 10, and 13 to recite the JAQ1 monoclonal antibody deposit accession number and claim 9 to be in parallel form with amended claims 3, 10, and 13. Applicant has amended the specification to specify the date on which the JAQ1 hybridoma was deposited along with the depository's address. These amendments do not introduce new matter, as discussed below. The claims under consideration stand rejected under one or more of 35 U.S.C. §§ 101, 112, 102, and 103. Applicant addresses each rejection according to its statutory origin.

Rejection Under 35 U.S.C. § 101

The Office rejects claims 11-13 under 35 U.S.C. § 101 for allegedly reciting a use without reciting any steps. To facilitate prosecution and clarify the claimed invention, Applicant has amended independent claim 11 to recite a method in which "an active principle that induces an irreversible inactivation or degradation of a collagen receptor on thrombocytes is combined with a pharmaceutically acceptable carrier." The specification supports this amendment at page 3, lines 13-15 and page 7, line 11. Thus, this amendment does not introduce new matter.

Because claim 11 now recites method steps, Applicant requests that the Office withdraw its rejection of claim 11 and claims 12 and 13, which depend on claim 11.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-5 and 11-13 stand rejected as allegedly indefinite for reciting the term "active principle." According to the Office, the term "principle" is not known in the art

and refers to a chemical ingredient rather than a biological ingredient. Applicant notes that the American Heritage College Dictionary defines the term "principle" as "a quality or an element determining intrinsic nature or characteristic behavior." In the context of the invention, the intrinsic nature is the ability to induce irreversible inactivation or degradation of a collagen receptor on thrombocytes. Moreover, the specification states at page 3, lines 16-17, that the active principle may be a chemical agent or an antibody, which is a type of biological agent. Thus, claims 1-5 and 11-13 are clear in that an active principle refers to an element (e.g., an antibody or a chemical) that determines the ability to induce irreversible inactivation or degradation of a collagen receptor on thrombocytes. Accordingly, Applicant requests that the Office withdraw this rejection.

The Office rejects claim 1 as allegedly indefinite because the Office finds it unclear how the active principle would degrade a collagen receptor or whether the active principle has proteolytic activity. Applicant refers to the specification, at pages 12 and 13, summarizing the data that shows the GPVI receptor missing from platelets in JAQ1 treated mice. In particular, at page 13, lines 16-21, the specification provides:

> [f]urthermore, the decreasing signals for both GPVI and JAQ1 after 24 and 48 h strongly suggest that the internalized complex was degraded in the intracellular compartments. GPVI belongs to the immunoglobulin superfamily and is closely related to immunoreceptors, some of which may become internalized when stimulated appropriately . . . .

Thus, the degradation referred to in claim 1 pertains to the degradation that results from a surface protein being internalized for destruction by the intracellular machinery. Applicant requests that the Office withdraw its rejection of claim 1.

Claims 3, 5, 10, 13, and 14 stand rejected as allegedly indefinite for reciting "JAQ1" without providing any other identifying characteristics. The Office suggests that

these claims be amended to include this monoclonal antibody's deposit Accession Number DSM ACC 2487. Applicant assumes that the Office did not intent to include claim 14, as there are currently only 13 pending claims. To facilitate prosecution, Applicant has amended claims 3, 10, and 13 as suggested. By virtue of its dependence on claim 3, claim 5 also incorporates this deposit information. Thus, the Office should withdraw this rejection.

The Office rejects claims 11-13 as indefinite for allegedly reciting a use without providing any steps involved in the use. Applicant refers the amendment of claim 11 above, which provides these steps. Thus, Applicant has rendered this rejection moot.

Claim 10 stands rejected as allegedly indefinite because the term "monoclonal antibody" apparently has no preceding article. To facilitate prosecution and clarify the claimed invention, Applicant has amended claim 10 to recite "a monoclonal antibody. . . ." Accordingly, Applicant requests that the Office withdraw this rejection of claim 10.

Rejections Under 35 U.S.C. § 112, First Paragraph

Enablement

The Office rejects claims 1-6 and 9-13 as allegedly not enabled on several grounds. First, according to the Office, the JAQ1 monoclonal antibody is required to practice the claimed invention and should be available to the public. Applicant notes that the specification at page 3, line 22 indicates that the hybridoma expressing the JAQ1 antibody was deposited under the Budapest Treaty. This deposit with the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH ("DSMZ") would not have been possible under the Treaty if Applicant had not agreed to make the hybridoma publicly available upon issuance of a patent and to maintain the culture for the required

period of time. Nonetheless, to facilitate prosecution, Applicant attaches a Declaration executed by Dr. Hugo Pfeil, Applicant's counsel, verifying that the JAQ1 hybridoma was deposited under the Budapest Treaty and will be made available according to the requirements of 37 C.F.R. § 1.806 should a patent issue from the instant application.

The Office also suggested that Applicant amend the specification to indicate the depository's address and the date of deposit. To facilitate prosecution, Applicant has amended the specification accordingly.

The Office's second ground for the alleged lack of enablement of claims 1-6 and 9-13 is that, according to the Office, the specification does not enable *any* medicament that induces an irreversible inactivation on *any* collagen receptor, using *any* active principle or *any* antibody. Specifically, the Office believes that claiming biochemical molecules by their activities does not provide sufficient guidance as to how to make them. The specification at page 5, the Office suggests, does not provide guidance for making any antibody with the claimed characteristics. Applicant respectfully traverses.

The specification should be interpreted in light of what was known in the art at the time of filing. Nieswandt et al. (*J. Biol. Chem.* 275:23998 (2000); "Nieswandt"), reference number 15 in the specification, provides a protocol on how the JAQ1 monoclonal antibody was prepared. Moreover, Applicant notes that, in item 13 of the Office Action, the Office acknowledges that the Nieswandt reference contains a method of making the antibody. Thus, the specification does enable claims 1-6 and 9-13 when considered in the context of what was known in the art.

Third, the Office asserts that the specification does not give guidance as to which collagen receptor is inactivated or to which collagen receptor the JAQ1 antibody binds.

In making this argument, the Office relies on Schulte et al. (*J. Biol. Chem.* 276:364-68 (2001); "Schulte") for the proposition that there allegedly may be a GPVI-independent receptor. Applicant asserts that Schulte's speculation as to the existence of second GPVI-independent receptor, is merely one more possible example of a collagen receptor that may be targeted by the active principle of claim 1. Though Applicant need not specify exactly which collagen receptors the active principle of claim 1 acts on, the specification does mention several in addition to Schulte's proposed GPVI-independent receptor. See specification at page 1, lines 25-28. Claim 1 recites "inactivation or degradation of a collagen receptor" and the specification provides several examples of such receptors. Methods for determining whether a receptor has been inactivated or degraded are known in the art and used in the specification. See for example, page 12, line 32 to page 13, line 12. The skilled artisan can readily adapt these methods to analyzing the expression of another collagen receptor.

Fourth, the Office believes that there is insufficient guidance as to which epitopes on the GPVI collagen receptor can induce an active principle that can inactivate or degrade the receptor on the surface of thrombocytes. Applicant notes that the specification explains, at page 13, lines 32-34, that the JAQ1 monoclonal antibody recognizes an epitope that is identical to or close to the CRP binding site on the GPVI receptor. With that level of guidance, it would not require undue experimentation for the skilled artisan to determine the exact epitope that the JAQ1 monoclonal antibody binds to, and thus, one example of such an epitope. Moreover, the skilled artisan could use, for example, competition experiments to determine whether a new antibody binds the same epitope or a similar epitope to that bound by JAQ1. If the new antibody prevents

labeled JAQ1 from binding to a target protein like GPVI, then the new antibody may bind the same or a similar epitope. These competition assays are well known in the art and are not difficult to perform.

Finally, the Office's last ground for a lack of enablement entails an alleged lack of proof that the claimed medicament would function to protect against thrombotic diseases. The Office acknowledges the mouse model for pulmonary thromboembolism presented in the specification at pages 11 and 12. Office Action at page 5. But it is not clear to the Office how this mouse model reflects the efficacy of protection against mammalian thrombotic diseases. The skilled artisan, the Office believes, could not predict the success of the claimed medicament based on the provided mouse model for thromboembolism.

Applicant contends that the teaching of the specification as a whole would lead a skilled artisan to reasonably conclude that the claimed medicament does protect against thrombotic disease. Nieswandt notes that "the mechanisms leading to collagen-induced platelet activation are similar in mice and humans." See page 24002, left column. Fibrillar collagen is the most thrombogenic component of the vascular subendothelium, as it supports platelet adhesion and activation, providing a role for collagen in thrombotic disease. Specification at page 1, lines 21-23. Moreover, the specification also notes at page 2, lines 12-16, that platelets from GPVI-deficient patients show severely impaired responses to collagen and that platelets from mice lacking the GPVI receptor do not aggregate in response to collagen. Furthermore, the JAQ1 monoclonal antibody not only binds to mouse GPVI, it also binds to the human GPVI receptor, suggesting that this antibody could be used therapeutically in humans. Specification at

page 3, lines 10 and 11. Finally, the pulmonary thromboembolism model clearly demonstrated complete protection from death due to thrombosis and cardiac arrest. All of the JAQ1 antibody-treated mice survived while 95% of the control mice died. Specification at page 11, lines 28-35. Thus, in light of all of the specification's teachings, the skilled artisan would conclude that an active principle targeting the interaction between platelets and collagen would protect against thrombotic disease.

Requiring data from human clinical trials to satisfy the enablement requirement is outside the domain of the USPTO. In the absence of human trials, animal models are commonly used to predict and assess the effectiveness of a treatment on a particular class of disease. The U.S. Court of Appeals for the Federal Circuit has addressed a related issue with respect to developing a drug for clinical use. The Court clearly indicated that testing for the full safety and effectiveness of a potential drug in clinical trials is more properly left to the FDA and that such testing is not required by Title 35 in the context of Office proceedings. *See In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) (citing *Scott v. Finney*, 34 F.3d 1058, 32 U.S.P.Q.2d 1115 (Fed. Cir. 1994)). By invoking these issues, the Office is confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *Id.* at page 1567. The Court further reasoned that

> one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans.

Id. The Court's rationale with respect to drug development is of equal import to the development of medicaments for protecting against a particular condition. As discussed above, none of the mice treated with the JAQ1 antibody died of cardiac arrest. For all the reasons set forth above, claims 1-6 and 9-13 are enabled. Applicant requests that the Office withdraw its rejection of these claims.

Written Description

Claims 1-6 and 10-13 stand rejected for allegedly lacking written description support in the specification. According to the Office, the specification discloses only anti-GPVI antibodies and the JAQ1 monoclonal antibody. The written description requirement for a claimed genus, the Office believes, may be satisfied through disclosure of a variety of elements, among them the relevant, identifying characteristics such as structure, physical properties, or chemical properties. Applicant traverses.

Applicant was in possession of the invention as claimed in independent claims 1, 6, and 10. The JAQ1 monoclonal antibody is only one example of the claimed invention. Applicant identified several characteristics of this monoclonal antibody, among them: (1) that this antibody could bind to the GPVI collagen receptor; (2) that this antibody also mediated the inactivation of the receptor or degradation of the receptor such that the receptor was removed from thrombocytes; and (3) that this antibody could protect mice from death due to thrombosis due to cardiac arrest. In identifying these properties, Applicant also recognized the broader concept of an agent that could interfere with a collagen receptor's ability to cause a thrombotic disease by inactivating that collagen receptor or causing it to be degraded or depleted from a thrombocyte's surface. See specification at page 3, lines 13-15 and page 18, lines 15-18. Thus, in

accordance with the written description requirement as outlined by the Office, Applicant has disclosed several identifying characteristics that comprise the genus of claim 1. Accordingly, claims 1-6 and 10-13 are supported by the specification and this rejection should be withdrawn.

Rejections Under 35 U.S.C. § 102

The Office rejects claims 1-4 and 9-13 under 35 U.S.C. § 102(b) as allegedly anticipated by Nieswandt. According to the Office, this reference teaches the JAQ1 monoclonal antibody, a method of producing it, and medicaments comprising the antibody. Applicant contends that Nieswandt is not prior art under 35 U.S.C. § 102(b). Under 35 U.S.C. §§ 119(a) and 120, the instant application has an effective U.S. filing date of January 23, 2001. Under 35 U.S.C. § 102(b), the invention must be "described in a printed publication in the United States or a foreign country . . . more than one year prior to the date of the application for patent in the United States." In this case, the cutoff date for § 102(b) purposes would be January 23, 2000. The Nieswandt reference was published on August 4, 2000, after the cutoff date.

Claims 1, 2, 4, and 11 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Clemetson et al. (*J. Biol. Chem.* 274:29019-24 (1999); "Clemetson"). According to the Office, Clemetson teaches a medicament comprising polyclonal antibodies and Fab fragments against collagen receptor GPVI and methods for preparing the medicament. The Office then refers to a later reference, Schulte et al. (*Blood* 101:3948-52 (2003); "Schulte2") to allegedly show that the characteristic of irreversible inactivation or degradation recited in claim 1 is inherent in anti-GPVI antibodies.

Applicant contends that the Office improperly uses Schulte2 as extrinsic evidence to show what one of ordinary skill in the art would understand Clemetson to disclose at the time of the invention. Schulte2 is not prior art and therefore cannot reflect what the skilled artisan knew at the time of the invention. Moreover, the alleged conclusion in Schulte2 that anti-GPVI agents may generally induce down-regulation of the GPVI receptor *in vivo* was made in reference to the antibodies studied, namely JAQ1, JAQ2, and JAQ3, rather than literally all anti-GPVI agents. Thus, this conclusion should be limited to the activities of those antibodies addressed in Schulte2 and does not support the Office's position of inherency of the property of receptor down-regulation for all anti-GPVI agents. As Clemetson does not teach irreversible inactivation or degradation of a collagen receptor, this reference cannot anticipate claims 1, 2, 4, and 11. Applicant therefore requests that the Office withdraw this rejection.

Claims 1, 2, 4, 11, and 12 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Busfield et al. (U.S. Patent 6,245,527; "Busfield"). The Office believes that Busfield teaches anti-GPVI antibodies, that GPVI modulators can be used to control thrombotic or hemorrhagic disorders, a method of making such antibodies, and a preferred dosage of antibodies. The Office uses Schulte2 as described above to allegedly show that the feature of irreversible inactivation or degradation of a collagen receptor on thrombocytes is inherent in Busfield's antibodies.

As the Office acknowledges, Busfield does not address the concept of irreversible inactivation or degradation of a collagen receptor on thrombocytes and therefore does not teach every element of the rejected claims. As Applicant explained above, Schulte2 is not prior art against the instant application and cannot reflect what

the skilled artisan knew at the time of the invention. Therefore, Busfield does not anticipate claims 1, 2, 4, 11, and 12. Applicant asks the Office to withdraw this rejection.

Rejections Under 35 U.S.C. § 103

The Office rejects claims 1 and 5 as allegedly obvious over Nieswandt in view of Owens et al. (*J. Immunol. Meth.* 168:149-65 (1994); "Owens"). The Office uses Nieswandt as discussed above at page 14 and relies on Owens for its alleged teaching that murine antibodies can be modified to different forms such as chimeric antibodies or humanized antibodies. As Applicant noted above, Nieswandt is not prior art against the instant application and therefore cannot be used as a basis for rejecting the claims as allegedly obvious. Moreover, Owens contains no teaching of active principles that irreversibly inactivate or degrade a collagen receptor. Thus, Owens alone cannot make the invention of claims 1 and 5 obvious. Applicant requests that this rejection be withdrawn.

The Office rejects claim 6 as allegedly obvious over Nieswandt, Clemetson, or Busfield in view of Conklin et al. (U.S. Patent 6,406,888; "Conklin"). The Office applies Nieswandt, Clemetson, and Busfield as discussed above, generally for their alleged teaching of polyclonal or monoclonal antibodies against GPVI. Claim 6 recites a labeled antibody. According to the Office, Conklin teaches that antibodies can be attached to other compounds, including tags or labels for use in diagnostic methods. Applicant traverses.

No combination of these references render claim 6 obvious. As discussed above, Nieswandt is not prior art against the instant application. Regarding Clemetson

and Busfield, neither of these references teach the concept of an anti-GPVI monoclonal antibody or polyclonal antibody that binds the epitope of the JAQ1 monoclonal antibody. Specifically, Clemetson's polyclonal antibodies do not bind the same epitope as the JAQ1 monoclonal antibody. Clemetson reported two forms of GPVI, one 65kD and the other 60kD, suggesting that the 60kD band was a proteolytic fragment of the 65kD band. See page 29020, right column under the Results section. Clemetson's polyclonal antibodies recognized the 65kD band. See page 29021, left column. In contrast, the JAQ1 antibody binds a protein of approximately 60kD. Specification at page 2. Regarding Conklin, this reference does not teach anti-GPVI antibodies at all. Thus, neither Clemetson, Busfield, nor Conklin, either alone or in combination make the invention of claim 6 obvious. Applicant requests that this rejection be withdrawn.

Finally, the Office rejects claims 11 and 12 as allegedly obvious over Clemetson in view of Harlow ("Antibodies, a Laboratory Manual" Cold Spring Harbor Press 1989; "Harlow"). The Office applies Clemetson as discussed above and relies on Harlow for the alleged teaching of general methods for producing antibodies. The Office believes that it would have been obvious for the skilled artisan to produce a monoclonal antibody using Harlow's method with the immunogenic fragment allegedly taught by Clemetson.

Applicant respectfully contends that the Office has misconstrued the meaning of claims 11 and 12. These claims do not pertain to the production of antibodies. Rather, these claims pertain to a method of preparing a medicament using an active principle, for example an antibody. Thus, the Office's rejection has no bearing on the invention of claims 11 and 12 and should be withdrawn.

Conclusions

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of claims 1-6 and 9-13.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: May 12, 2005

By: _____
Maryann T. Puglielli
Reg. No. 52,138

Attachments: Deposit Declaration